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Interplay of p16/Rb Loss and Viral Integration in Precursor Lesions of Cervical Cancer

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ABSTRACT

Persistent HPV infection drives carcinogenesis via E6/E7 targeting p53 and Rb inactivation; loss of the p16 gatekeeper amplifies cellular susceptibility to HPV integration, rapidly accelerating progression toward invasive disease, defining critical targets for therapeutic precision and risk stratification. This narrative review rigorously synthesized literature from PubMed, Scopus, and other databases using combined MeSH terms and keywords like "cervical cancer" AND "HPV" AND "p16 expression," filtering for English-language, full-text articles indexed before January 2026, explicitly excluding editorials and non-human studies via initial screening followed by full-text assessment focused solely on molecular pathogenesis linking viral oncogenesis to host cell cycle control in precursor lesions. High-risk HPV infection drives cervical carcinogenesis through E6 and E7 oncogenes, which degrade p53 and inactivate Rb, leading to uncontrolled proliferation reflected by compensatory p16 overexpression, a robust biomarker for high-grade disease. Viral integration is a critical step, often disrupting host genes like CDKN2A while locking in high E6/E7 expression, creating genomic instability. Clinically, p16 status helps triage positive HPV tests to identify high-risk lesions; while CDK4/6 inhibitors offer therapeutic avenues, primary vaccination remains the definitive strategy by eliminating the initiating oncogenic stimulus.

Introduction

Cervical cancer, a significant global health concern, remains a leading cause of cancer-related mortality among women worldwide. While progress in screening and vaccination programs has demonstrably reduced the incidence of cervical cancer caused by Human Papillomavirus (HPV), a substantial burden persists, particularly in resource-limited settings. Understanding the intricate interplay of molecular alterations driving cervical carcinogenesis is paramount for developing more effective prevention, diagnosis, and therapeutic strategies (1). This review delves into the critical relationship between the loss of retinoblastoma protein (p16) and its downstream target, the retinoblastoma protein (Rb), and the integration of HPV DNA within precursor lesions of the cervix. We will explore the molecular mechanisms underlying this complex interaction, its role in promoting cellular transformation, and its implications for risk stratification and personalized treatment approaches (2).The pathogenesis of cervical cancer is a multistep process, typically initiated by persistent infection with high-risk HPV types, primarily HPV16 and HPV18. These oncogenic HPV types encode proteins, notably E6 and E7, which disrupt crucial cellular regulatory pathways, driving uncontrolled cell proliferation and ultimately leading to malignant transformation (3). The E6 protein binds to and ubiquitinates p53, a key tumor suppressor protein known as the "guardian of the genome." This ubiquitination targets p53 for proteasomal degradation, effectively silencing its tumor suppressor functions, including cell cycle arrest, apoptosis, and DNA repair (4). Concurrently, the E7 protein binds to and inactivates Rb, a critical regulator of the G1/S cell cycle transition. Rb normally binds to transcription factors like E2F, preventing their activation and thereby halting cell cycle progression (5). When Rb is phosphorylated by cyclin-dependent kinases (CDKs) upon E7 inactivation, E2F is released, enabling the transcription of genes required for S-phase entry and promoting uncontrolled proliferation (6).

The inactivation of both p53 and Rb represents a pivotal event in cervical carcinogenesis. Loss of p53 function leads to genomic instability, increased mutation rates, and impaired DNA repair mechanisms, further accelerating the accumulation of oncogenic alterations. Rb inactivation removes a critical brake on the cell cycle, allowing cells with accumulated DNA damage to proliferate unchecked (7). The synergistic effects of p53 and Rb inactivation

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create a permissive cellular environment for further genomic alterations, ultimately driving the progression from precancerous lesions to invasive cancer (8).

While HPV E6 and E7 proteins exert a dominant influence on cervical carcinogenesis, the cellular context plays a significant role in shaping the disease trajectory. A particularly important aspect of this context involves the expression and function of p16INK4a, a cyclin-dependent kinase inhibitor that acts as a critical gatekeeper at the G1/S checkpoint (9). p16INK4a binds to and inhibits CDK4 and CDK6, preventing the phosphorylation of Rb and thus maintaining Rb's tumor suppressor function. Loss of p16INK4a expression, often due to epigenetic silencing through promoter hyper methylation, results in Rb hyper phosphorylation and subsequent E2F activation, contributing significantly to uncontrolled cell proliferation in cervical precursor lesions (10). The loss of p16, therefore, creates a "perfect storm" for malignant transformation, amplifying the effects of E6 and E7(11).

The interplay between p16/Rb loss and HPV integration is complex and bidirectional. The integration of HPV DNA into the host genome can directly disrupt the expression of tumor suppressor genes, including p16. Integration at specific genomic loci can lead to the physical disruption of the p16 gene, preventing its transcription (12). Furthermore, HPV integration can activate oncogenes or disrupt the function of other tumor suppressor pathways, indirectly contributing to p16 loss. Conversely, loss of p16 can create a cellular environment more susceptible to HPV integration (13). The disruption of the G1/S checkpoint by p16 loss increases genomic instability and allows for more efficient integration of HPV DNA, further accelerating the carcinogenic process (14).

The significance of p16/Rb loss and HPV integration extends beyond the development of precancerous lesions. These alterations are also predictive of disease progression and response to therapy. Patients with cervical cancer exhibiting loss of p16 expression or high levels of HPV integration often have a poorer prognosis (15). Moreover, the presence of p16 loss can influence the response to certain chemotherapeutic agents. Understanding these complex interactions is critical for developing targeted therapies that can effectively address the molecular drivers of cervical cancer (16).

This review will delve deeper into the molecular mechanisms linking p16/Rb loss and HPV integration, exploring the epigenetic and genetic factors that contribute to these alterations. We will discuss the role of various signaling pathways, including those involving cyclin-dependent kinases, and the impact of these alterations on cell cycle regulation, DNA repair (17), and apoptosis. Furthermore, we will examine the clinical implications of p16/Rb loss and HPV integration, focusing on their prognostic value, their role in treatment response, and their potential as therapeutic targets (18).

Material and methods

This narrative review systematically gathered relevant literature by querying major electronic bibliographic databases, including PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. The search strategy employed a combination of medical subject headings (MeSH terms) and free-text keywords to maximize capture of relevant studies pertaining to cervical carcinogenesis, HPV oncogenes (E6/E7), p16, and the Rb pathway. Specific search strings included combinations such as: "cervical cancer" AND "HPV" AND "p16 expression," "HPV E7" AND "Rb degradation," and "CIN" AND "p16/Rb axis." Only articles published in the English language, with full-text availability, and indexed before January 1, 2026, were considered for inclusion. Exclusion criteria primarily involved case reports, editorials, non-peer-reviewed abstracts lacking full methodology, and studies focusing exclusively on non-human models or vaccines without detailing molecular pathogenesis.

Results

p16/Rb Pathway Dysregulation in Cervical Precursor Lesions

Cervical cancer remains a significant global health disparity, persisting as a leading cause of cancer-related mortality, particularly in low- and middle-income countries, despite the existence of effective prophylactic vaccines. The overwhelming causality in virtually all cervical cancer cases is directly attributable to persistent infection by high-risk human papillomavirus types, most notably HPV-16 and HPV-18(19). The progression from initial hrHPV infection to the development of high-grade squamous intraepithelial lesions, or cervical intraepithelial neoplasia grade 3, and ultimately invasive carcinoma, constitutes a well-defined, multi-step carcinogenic cascade. This process is fundamentally driven by the integration of the viral genome into the host cell's DNA, leading to the constitutive expression of two primary oncogenes: E6 and E7(20). These viral proteins act as master disruptors of essential host cell cycle and apoptotic machinery. E6 targets the tumor suppressor p53 for proteasomal degradation, thereby abrogating cell cycle arrest and apoptosis in response to DNA damage. Concurrently, E7 targets the retinoblastoma protein Rb, the gatekeeper of the G1 to S phase transition. By binding Rb and promoting its degradation, E7 effectively releases the E2F transcription factors, forcing the cell into uncontrolled proliferation a state termed oncogene-induced replication stress (21). The critical diagnostic and prognostic hallmark reflecting this disruption in the Rb pathway is the dramatic and sustained upregulation of the CDKN2A-encoded protein p16INK4a. In an effort to compensate for E7-mediated Rb inactivation, the cell overproduces p16, which serves as a robust surrogate biomarker for active high-risk HPV oncogene expression and definitive histologic transformation, making p16 immunohistochemistry a cornerstone in assessing the biological significance of underlying HPV infection in precursor lesions (22) (figure 1).

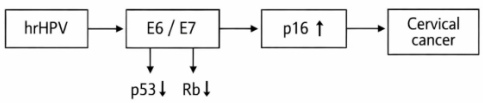

Figure 1. cervical carcinogenesis pathway

The central premise of current research in cervical carcinogenesis pivots on the precise molecular dialogue between these viral drivers and the hosts genetic response, specifically focusing on the p16/Rb axis within the context of viral integration. While p16 overexpression serves as an excellent marker for established hrHPV activity, the mechanistic depth required for precision diagnostics necessitates a deeper interrogation of the host-pathogen interface (23). Therefore, the objective of this investigation is to meticulously examine the reciprocal relationship between the functional status of the p16/Rb pathway and the molecular events associated with HPV genome integration in CIN lesions. Specifically, we aim to correlate patterns of p16 expression, which indicate the degree of Rb pathway perturbation, with the physical state of the HPV DNA namely, whether it remains episomal or becomes integrated across the spectrum of pre-invasive disease (24). Understanding how the intensity of E6/E7 activity translates into the magnitude of p16 induction and whether p16 integrity can predict the transition toward stable, high-risk integration will provide refined criteria for triaging patients with persistent HPV positivity (25).

The Viral Oncogenic Mechanism: HPV E6 and E7 Functions

The oncogenic potential of high-risk Human Papillomaviruses (HPV), particularly types 16 and 18, is fundamentally mediated by the sustained expression of two key viral proteins: E6 and E7, which act in concert to subvert critical host cell cycle checkpoints and apoptotic pathways. The E6 protein executes its primary transforming function through the targeted degradation of the tumor suppressor protein p53, often referred to as the guardian of the genome. E6 achieves this by binding directly to the cellular ubiquitin ligase E6AP (UBE3A), forming a complex that recognizes p53 as a substrate for proteasomal destruction (26). This binding event bypasses the normal regulatory mechanisms that stabilize p53 in response to cellular stress, DNA damage, or oncogenic signaling. The resulting dramatic decrease in functional p53 levels abolishes the cell's ability to enforce cell cycle arrest at the G1/S or G2/M checkpoints, prevents DNA repair processes dependent on p53 transcriptional activity, and crucially, inhibits p53-mediated apoptosis in the presence of accumulating genomic aberrations (27). The loss of p53 function licenses the cell to continue proliferation despite significant genotoxic stress, establishing the first critical component of cellular immortalization and genomic instability necessary for malignant progression. Furthermore, E6 has been shown to interact with other cellular targets, including PDZ domain-containing proteins, contributing to disruption of cell polarity and enhanced telomerase activity, though its central role remains the unchecked elimination of p53 (28).

The second, equally vital component of the HPV oncogenic mechanism is executed by the E7 protein, which specifically targets the Retinoblastoma protein (Rb), the master regulator of the G1 to S phase transition. E7 binds to the pocket domain of the Rb protein with high affinity. This binding event mimics the action of host-cell cyclin-dependent kinases (CDKs) that normally phosphorylate Rb in late G1. Phosphorylation of Rb causes its conformational change, leading to its dissociation from the E2F family of transcription factors (29). In the context of E7-mediated inactivation, the binding of E7 directly sequesters Rb or promotes its degradation, effectively liberating the bound E2F transcription factors. Free E2F then translocates to the nucleus to drive the transcription of genes essential for DNA synthesis and cell cycle progression, such as cyclins E and A, DHFR, and CDC2. By constitutively activating the E2F pathway, E7 forces the cell into the S phase, independent of external growth signals, thereby overriding the primary brake on cellular division. The synergistic effect of E6 neutralizing p53 preventing apoptosis in response to hyper proliferation and E7 liberating E2F driving hyper proliferation constitutes the prototypical "Double Hit" hypothesis against major tumor suppressor pathways (figure 2) (30). This dual disruption of the p53 and Rb axes provides the fundamental molecular underpinning for the uncontrolled cellular growth and accumulation of damage characteristic of HPV-driven carcinogenesis, particularly in precursor lesions like Cervical Intraepithelial Neoplasia (CIN) (31).

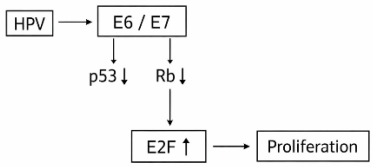

Figure 2. HPV E6/E7 double-hit mechanism

The Host Cell Cycle Regulator: p16INK4a and Rb Pathway

The p16INK4a protein serves as an indispensable guardian of the host cell cycle, operating upstream of the Retinoblastoma (Rb) protein within the critical G1 restriction point mechanism. Functionally, p16INK4a is a potent cyclin-dependent kinase inhibitor (CKI) belonging to the INK4 family, specifically designed to inhibit the activity of CDK4 and CDK6 complexes. These kinases, when active and bound to Cyclin D, are responsible for initiating the hyper phosphorylation cascade targeting the Rb protein (32). In its normal, unperturbed state, the cell maintains sufficient p16INK4a expression, which sequesters and inactivates CDK4/6. This sustained inhibition prevents the phosphorylation of Rb, thereby maintaining Rb in its active, hypo phosphorylated state. In this active configuration, Rb tightly binds to and sequesters the E2F family of transcription factors, effectively halting the transcription of genes required for DNA replication and entry into the S phase (33). This checkpoint acts as a crucial fail-safe, ensuring that the cell only proceeds into proliferation when appropriate growth signals are present and the genome is intact. The preservation of Rb in its active, growth-repressive conformation, mandated by functional p16INK4a, is therefore paramount for preventing premature cell cycle entry and the propagation of genomic errors. The pathway's integrity is constantly challenged by oncogenic

stressors, such as uncontrolled expression of cyclins or viral oncoproteins, making the status of p16INK4a expression a critical determinant of cellular fate; its functional loss removes the primary inhibitory constraint on CDK4/6 and thus unleashes E2F-driven transcription, overriding the G1 safeguard (34).

In the context of precancerous lesions, such as those induced by high-risk HPV, the integrity of this regulatory axis is frequently compromised through various mechanisms that lead to the functional inactivation or loss of p16INK4a expression, often preceding or accompanying the direct action of viral proteins like E7. While HPV E7 directly binds and inactivates Rb, rendering p16INK4a somewhat redundant for immediate G1 release, the independent epigenetic silencing of the CDKN2A locus which encodes p16INK4a represents a convergent and highly significant pathway for tumor progression, particularly in later stages or in other cancer types that mimic HPV-driven events (35). The primary mechanism for this functional loss is hyper methylation of the p16INK4a promoter region, an epigenetic modification that leads to transcriptional repression and subsequent absence of the protein. Additionally, homozygous deletions or large-scale genomic loss events encompassing the CDKN2A locus on chromosome 9p21 result in complete gene ablation (36). The loss of p16INK4a function, regardless of the upstream cause (HPV-independent mutation or methylation), results in the constitutive activation of CDK4/6, leading to Rb hyper phosphorylation, E2F release, and uncontrolled cell cycle progression. Immunohistochemically detection of p16 accumulation, paradoxically, is often used as a surrogate marker for high-risk HPV infection because the viral E7 protein inactivates Rb, which in turn triggers a compensatory feedback loop leading to the overexpression of p16 in many precursor lesions, although true loss of function via methylation or deletion represents a more definitive, HPV-independent oncogenic event driving tumor maintenance (37).

Viral Integration and Genomic Instability

The integration of the high-risk Human Papillomavirus (HPV) DNA into the host cell genome represents a critical, non-reversible transition point in the trajectory from low-grade cervical intraepithelial neoplasia (CIN 1) to high-grade lesions (CIN 2/3) and invasive carcinoma. This event, which occurs in approximately 80% of invasive cervical cancers, fundamentally alters the viral life cycle; the viral genome is fractured, leading to the loss of the upstream regulatory E2 gene, which normally represses the transcription of the oncogenes E6 and E7(38). A particularly consequential effect is the direct interruption or dysregulation of host genes located near the integration site, most notably the CDKN2A locus encoding the tumor suppressor p16INK4a. When HPV integrates near or into this critical gene, the structural damage can lead to its functional inactivation, thereby contributing synergistically to the loss of G1 checkpoint control initiated by viral oncoproteins (39). Furthermore, the insertion often places the remaining E6/E7 expression cassette under the control of strong, constitutively active host cell promoters, leading to massive overexpression of these oncogenes, which surpasses the levels typically seen in episomal infections where viral gene expression is tightly regulated by the viral enhancer/promoter system. This elevation in E6 and E7 activity is the molecular engine driving malignant transformation (40).

The persistent, high-level expression of the HPV oncoproteins E6 and E7 following integration directly dictates the severity and progression potential of the lesion by overwhelming the host cell's natural defense mechanisms. The E7 oncoprotein's primary and most potent function is the binding and subsequent proteasomal degradation of the Rb protein, effectively neutralizing its ability to sequester E2F transcription factors. With Rb functionally eliminated, the cell is perpetually driven into S phase, regardless of external signals or the presence of DNA damage, creating a state of unchecked proliferation that defines high-grade dysplasia (41). Concurrently, E6 targets the p53 tumor suppressor for ubiquitin-mediated degradation, abrogating the critical G1/S and G2/M checkpoints that would normally halt cell division in response to DNA damage or cellular stress damage that is exacerbated by the integration process itself and the resulting genomic chaos. Therefore, HPV integration serves as a dual-hit event: it creates new genetic vulnerabilities by disrupting host genes and simultaneously locks in the expression of viral factors (E6/E7) at high levels that guarantee the inactivation of both the Rb and p53 pathways (42). This sustained, aggressive subversion of the two major tumor suppression networks explains why integration marks the transition to irreversible malignancy, as the cells gain the hallmark capabilities of uncontrolled growth and resistance to apoptosis necessary for invasive behavior (43) (figure 3).

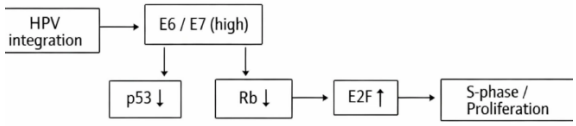

Figure 3. HPV integration and the Double Hit oncogenic mechanism

The Interplay: Synergistic Effects in Precursor Lesions

The progression from persistent human papillomavirus (HPV) infection to invasive cervical cancer is not a single event but a cascade of molecular dysregulations, where the failure to adequately suppress viral oncogenes acts synergistically with host cell vulnerabilities. A crucial element in this progression is the functional status of the p16INK4a tumor suppressor. While HPV integration, as previously discussed, often directly causes p16 loss through genetic disruption, the functional inactivation of the p16/Rb axis can begin even before complete integration, during the early phases of high-grade cervical intraepithelial neoplasia (CIN 1) where the viral genome exists episomally. In these early stages, high expression of E7 can saturate the host's Rb capacity, even if p16 levels are near normal, leading to increased E2F release (44). However, a partial or early suppression of p16 expression, perhaps due to promoter methylation or epigenetic silencing distinct from viral integration, significantly lowers the threshold for sustained cell cycle deregulation. The reduced availability of p16 means that fewer CDK4/6 complexes are inhibited, leaving the cell more susceptible to the proliferative drive imposed by E7(45). More

importantly, the impairment of p16 function destabilizes the host cell's response to the genetic damage caused by integrating viral DNA. Cells with diminished p16 surveillance are less capable of enforcing a stable cell cycle arrest when HPV integration introduces chromosomal breaks or disrupts host genes, thereby promoting the survival and clonal expansion of cells that have undergone integration, accelerating the transition from CIN 2 to CIN 3 and invasive disease (46).

The clinical utility of understanding this interplay is most evident in pathological assessment through immunohistochemically staining for p16. In the context of cervical screening, strong, diffuse nuclear and cytoplasmic positivity for p16 serves as a robust surrogate biomarker for the biologically active presence of high-risk HPV oncogenes (E6/E7). In normal or transiently infected squamous epithelium, p16 staining is typically sparse or negative. Conversely, in precursor lesions where HPV is actively driving cell proliferation regardless of whether the viral genome is episomal or integrated the compensatory cellular response to E7-mediated Rb inactivation leads to a massive, detectable upregulation of p16(47). Therefore, the level of p16 expression directly correlates with the stage of neoplastic evolution: negative staining suggests a low-risk infection or transient infection, focal positivity is often seen in low-grade lesions, whereas diffuse and intense positivity is highly characteristic of high-grade lesions (CIN 2 and CIN 3) which harbor sustained, high-level oncogene expression. This strong correlation confirms that p16 overexpression is a consequence of active oncogenic signaling that precedes or accompanies the genomic instability associated with integration, making it an indispensable tool for differentiating clinically significant, persistent precursor lesions from benign changes (48).

Clinical and Diagnostic Implications

The integration of human papillomavirus (HPV) oncogenes (E6/E7) and the subsequent functional disruption of the p16/Rb pathway have profound implications for the clinical management and diagnostic stratification of cervical lesions. The interpretation of positive HPV test results, particularly in screening algorithms involving women over 30 years of age, often presents an ambiguity regarding the persistence and biological aggressiveness of the infection. Here, the quantitative or qualitative assessment of p16 expression provides essential context to resolve this uncertainty. When molecular testing indicates the presence of high-risk HPV DNA a finding that includes both transient, self-clearing infections and true persistent oncogenic processes the concurrent analysis of p16 provides essential context (49). A strong, diffuse positive result for p16 immunohistochemistry signifies that the viral oncogenes are actively driving cell cycle progression by overwhelming the Rb pathway. This active oncogenic state is strongly associated with true underlying high-grade precursor lesions (CIN 2 or higher) that possess a significant risk of malignant progression, irrespective of the initial HPV genotype or the exact HPV viral load detected. Conversely, HPV positivity in the absence of p16 overexpression suggests that the virus is largely episomal, latent, or that the cellular machinery is capable of effectively neutralizing the immediate oncogenic pressure, often classifying the finding as one associated with transient infection or low-grade abnormalities that rarely progress. Consequently, using p16 as a triage marker alongside primary HPV testing enhances the specificity of colposcopy referral, reducing unnecessary procedures for women with clinically insignificant infections while prioritizing those with biologically significant disease progression risk (50). Beyond initial triage, the status of p16 serves as a potent prognostic biomarker for predicting the natural history and potential advancement of confirmed precursor lesions. In situations where a biopsy reveals low-grade squamous intraepithelial lesions (LSIL), the presence of high p16 expression within the epithelial layer is a significant predictor that the lesion harbors underlying high-grade cytology or histology that may have been missed on initial sampling. This finding mandates closer follow-up or immediate escalation of management, as the molecular signature indicates an established oncogenic mechanism is at play, pushing the cells toward invasive carcinoma (51). Furthermore, the molecular landscape that includes high p16 expression is intrinsically linked to the tumor microenvironment and immune evasion mechanisms. High levels of p16 positivity are often observed concurrently with the infiltration of immune cells, such as cytotoxic T lymphocytes (CTLs), indicating that the body's immune system recognizes the transformed cells as abnormal and mounts an immune response. However, the very mechanisms of HPV carcinogenesis, particularly the sustained overexpression of E6 and E7, are known to induce a state of localized immunosuppression (52). E6 promotes the degradation of p53, which is essential for initiating effective apoptotic responses to immune surveillance, and E7 alters the expression of various immune recognition molecules. Therefore, while p16 staining acts as a visual marker of the oncogenic drive, the concurrent state of the microenvironment characterized by this immune response alongside viral evasion tactics determines the ultimate fate of the lesion, with persistent high p16 expression signaling a tumor that has successfully bypassed immune clearance mechanisms to sustain proliferation (53).

Therapeutic Opportunities

The integration of viral oncoproteins E6 and E7 namely the inactivation of p53 and Rb respectively present compelling, yet challenging, targets for therapeutic intervention in established cervical neoplasia. Given the success of CDK4/6 inhibitors such as palbociclib, ribociclib, and abemaciclib in treating hormone receptor-positive breast cancers by arresting the cell cycle at the G1 phase, a logical therapeutic hypothesis involves repurposing these agents in HPV-positive cervical cancers, where the Rb pathway is constitutively deactivated by E7(54). These inhibitors function by blocking the kinases (CDK4/6) that normally hyper phosphorylate Rb, thereby preventing the release of E2F transcription factors and halting uncontrolled proliferation. While E7's primary mechanism bypasses the direct requirement for CDK4/6 activity to phosphorylate Rb by binding to and destabilizing Rb itself, these inhibitors may still offer benefit by targeting alternative CDK pathways or by modulating the cellular environment that E7 has created. Preclinical studies have explored this concept, sometimes demonstrating synergistic effects when CDK4/6 inhibitors are combined with agents that target other viral or host survival pathways, such as those regulating p53 activity or overall proteasomal degradation. Furthermore, research into restoring p53 function or directly degrading the E6

oncoprotein offers a more upstream approach to reversing the oncogenic cascade (55). Direct targeting of E7 remains a significant hurdle due to the compact nature and diverse binding surfaces of this protein, but therapeutic strategies focusing on inhibiting the E7-Rb interaction via small molecule antagonists or novel peptide inhibitors are areas of active preclinical exploration. Ultimately, any successful therapy must overcome the resistance mechanisms inherent in established, often genomically unstable tumors, and address the immune evasion signature that allows these cancers to flourish despite localized immune surveillance (56).

However, the most profound and unequivocally successful intervention against HPV-driven carcinogenesis is not therapeutic but preventive. The development and widespread implementation of prophylactic HPV vaccines represent a monumental achievement in oncology, shifting the paradigm from treatment of invasive disease to the primary prevention of infection itself. These vaccines, targeting the highly immunogenic minor capsid protein L1 of oncogenic HPV types (most notably types 16 and 18), elicit robust, long-lasting humoral and cellular immune responses that prevent initial infection of the basal epithelial cells of the cervix, anus, and oropharynx. High vaccination coverage rates have already demonstrated a significant decline in the prevalence of high-risk HPV types and a corresponding reduction in the incidence of high-grade precancerous lesions (CIN 2/3) in vaccinated cohorts. This strategy effectively cuts off the initial oncogenic stimulus the persistent infection by E6/E7-expressing viruses thereby negating the entire subsequent cascade involving p53 degradation, Rb inactivation, and genomic instability. While therapeutic agents crucial for managing the existing burden of cervical cancer and precancerous lesions that occur in unvaccinated or inadequately screened populations, the continued global commitment to vaccination programs, coupled with effective secondary screening strategies for older populations, remains the most cost-effective and ethically sound approach to achieving the eventual elimination of cervical cancer as a public health problem.

Discussion

The most robust strategy against human papillomavirus associated cervical cancer remains primary prevention through widespread vaccination, which targets the capsid proteins L1 of the most oncogenic HPV types, preventing initial infection and subsequent oncogenic progression, a success story in public health that dramatically reduces the pool of susceptible individuals entering the high-risk category for precursor lesion development. However, for those individuals who harbor established high-grade lesions or already exhibit invasive cancer where E6 and E7 expression is driven by integrated viral DNA, targeted therapeutic interventions are essential, necessitating the direct neutralization of the viral oncoproteins or the restoration of cell cycle control. A highly promising avenue involves repurposing pharmaceutical agents known to be effective in other malignancies where cell cycle dysregulation is central, most notably CDK4/6 inhibitors such as palbociclib, ribociclib, and abemaciclib. These agents function by restoring the inhibitory brake on the cell cycle by binding to and inactivating the CDK4/6 kinases, thereby preventing the hyper phosphorylation of Rb irrespective of the presence of the E7 oncoprotein, forcing the cell back into a quiescent state or triggering senescence or apoptosis in high-risk clones that have become entirely dependent on the E7-driven Rb inactivation. Clinical trials involving these inhibitors in recurrent or metastatic cervical cancer, particularly that demonstrating high p16 expression confirming active pathway dependence, are actively underway to determine optimal dosing schedules and combination therapies, potentially overcoming the inherent resistance mechanisms that might arise from concurrent p53 loss. Further innovative strategies explore direct targeting of the viral oncogenes themselves, including the development of siRNA therapies designed to degrade the E6/E7 messenger RNA transcripts or small molecules capable of disrupting the binding interface between E7 and Rb. These approaches aim for a molecular cure by effectively silencing the viral engine driving the entire malignant process, offering hope for salvaging patients where conventional surgery or chemo radiation has failed to achieve complete disease eradication. The integration of these therapeutic advances with ongoing screening efforts and continued vaccination coverage forms the comprehensive framework for ultimately eliminating cervical cancer as a significant public health threat (56).

Conclusion

In conclusion, the trajectory of human papillomavirus driven cervical carcinogenesis underscores a dual pathway toward malignancy control: aggressive primary prevention and targeted molecular therapy. The monumental success of vaccination, by eliminating the initial oncogenic stimulus generated by the E6 and E7 oncoproteins, remains the foremost public health triumph, dramatically reducing the incidence of precursor lesions and subsequent invasive disease by eliminating the viral reservoir. Concurrently, for established or refractory cancers where viral integration has locked the cell cycle machinery into proliferation via E7-mediated Rb inactivation, targeted pharmacological interventions represent a critical secondary defense line. The clinical exploration of CDK4/6 inhibitors offers a rational therapeutic strategy, effectively bypassing the upstream viral manipulation to restore the tumor-suppressive functions of the Rb pathway, particularly in tumors exhibiting high p16 expression that signals dependence on this axis. As research advances toward direct neutralization of the viral transcripts or oncogene interaction sites, the ultimate goal is to solidify a therapeutic landscape where primary prevention minimizes need, while precision oncology offers definitive management options for breakthrough or persistent disease, ensuring cervical cancer moves definitively toward eradication across global health agendas.

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All authors of this article confirm the authenticity of the manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

Disclosure Statement

No potential conflict of interest reported by the authors.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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